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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,903	07/10/2001	Avi Ashkenazi	10466/69	1524

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HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CO 94025-3506

EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application N .	Applicant(s)	
	09/902,903	ASHKENAZI ET AL.	
	Examin r	Art Unit	
	Bridget E. Bunner	1647	

--The MAILING DATE of this communication appears on the cov r sheet with the correspondenc address --

THE REPLY FILED 20 October 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☐ The proposed amendment(s) will not be entered because:

(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Elizabeth C. Kemmerer

Claim(s) allowed: _____.

Claim(s) objected to: _____.

ELIZABETH KEMMERER
PRIMARY EXAMINER

Claim(s) rejected: *39-43*.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance because: Claims 39-43 are rejecte under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantia asserted utility or a well established utility. Novel biological molecules lack well established utility and must undergo extensive experimentation. Claims 39-43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for these rejections is set forth for claims 39-43 at pg 3-7 of the previous Office Action (19 May 2003).

Applicant asserts that the teaching in Example 70 of the specification is detailed and sufficient for one skilled in the art to determine effective concentrations for PRO293. To address the Examiner's concerns about "toxic concentrations of PRO293" and the specificity of the PDB12 assay, Applicant has enclosed a declaration by Dr. Jean-Phillipe Stephan, an expert in the PDB12 cell inhibition assay. Dr. Stephan explains that PDB12 cells tolerate and respond well to fairly high concentrations of proteins without dying or getting damage. Dr. Stephan also indicates that, regarding the instant application, those proteins that did not show any effect on the PDB12 cells could be considered as negative internal controls and demonstrate the specificity of the effects of proteins like PRO293. Finally, Dr. Stephan states that since PDBV12 cells are considered to potentially represent the pancreatic ductal progenitor cells, compounds that test positive in a PDB12 cell proliferation/inhibition assay are considered to potentially affect pancreative ductal (and possibly islet) cell progenitor functions in vivo. Applicant argues that a specific and substantial use for PRO293 polypeptides in treating pancreatic disorders, like diabetes has been asserted and therefore, no further research is required by the skilled artisan. Applicant also contends that since the level of skill in the art is high, one skilled in the art would know that agonistic PRO293 antibodies would be useful for treating such pancreatic disorders.

The declaration under 37 CFR 1.132 filed 20 October 2003 is insufficient to overcome the rejection of claims 39-43 based upon the lack of utility under 35 U.S.C. § 101 and the lack of enablement under 35 U.S.C. § 112, first paragraph as set forth in the last Office action. Specifically, although Dr. Stephan has indicated that the observed results in the PDB12 assay may not be due to non-specific damage of the PDB12 cells themselves, the declaration and the specification of the instant application do not teach any specific resulting cell numbers or percentages, statistical differences, or the number of repetitions for the assay. The declaration and specification also do not disclose the quantity of PRO293 that is utilized in the assay. It is recognized in the art that cell growth/inhibition assays usually implement a variety of concentrations of the compound or protein of interest. Dr Stephan's declaration only indicates that PDB12 cells respond to proteins up to a concentration of 100 micrograms/ml (point 5 of declaration). Therefore, due to little or no guidance in the specification, the skilled artisan could still conclude that PRO293 was utilized at toxic levels in the assay, which killed the PDB12 pancreatic ductal cells rather than showing an inhibition in protein production. Additionally, the specification does not teach any methods or working examples that utilize a different cell type or different growth factors/inhibitors as controls. According to the vague results listed in this example, one skilled in the art might predict that the pancreatic ductal cells simply started to naturally die off, with the PRO293 protein having no effect on cell inhibition/proliferation or inhibition of protein production. Furthermore, any slight decrease in protein production, which may even result from the normal variations in cell number, would not indicate that PRO293 specifically inhibits protein production. Without any specific knowledge, which could not be obtained from the instant specification, one of ordinary skill in the art at the time the invention was made would not have been able to use the information obtained from this assay in a useful manner. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial. Antibodies can be made to any polypeptide. However, if the specification discloses nothing specific and substantial about the polypeptide, therefore both polypeptide and their antibodies have no patentable utility.

Furthermore, although Dr. Stephan has extensive training and experience as a scientist in cell-based assays, Dr. Stephan has not investigated what effects administration of a protein or antibody, such as an anti-PRO293 antibody, has upon treatment of pancreatic disorders, such as diabetes. With regard to treatment or diagnosis o disease, in order for anti-PRO293 antibodies to be useful, as asserted, for treatment or diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the PRO293 polypeptide and a disease or disorder. Since the instant specification does not disclose the presence or association of the PRO293 with any specific cell or tissue, there is not sufficient evidence for establishing a utility in the treatment or diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the PRO293 polypeptide and the disease. There must be some expression pattern that

would allow the claimed polypeptide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the PRO293 polypeptide is either presen only in diseased tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed antibodies against the PRO293 polypeptide as diagnostics for diseases. However, in the absence of any disclosed relationship between the PRO293 polypeptides and any disease or disorder and the lack of any correlation between the claimed polypeptide with any known disease or disorder, any information obtained from a protein inhibition assay would only serve as the basis for further research on the observation itself.